IT IS CLAIMED:

1. A chimeric oligonucleotide having the formula 5'–W–X^1–Y–X^2–Z–3', where W represents a 5'-O-alkyl nucleotide;

each of X^1 and X^2 represents a block of seven to twelve phosphodiester-linked 2'-O-alkyl ribonucleotides;

Y represents a block of five to twelve phosphorothioate-linked deoxyribonucleotides; and

Z represents a blocking group effective to block nuclease activity at the 3' end of the oligonucleotide.

2. The oligonucleotide of claim 1, wherein the alkyl groups of the 5'-O-alkyl nucleotide and the 2'-O-alkyl ribonucleotides are lower alkyl groups.

3. The oligonucleotide of claim 2, wherein the alkyl groups of the 2'-O-alkyl ribonucleotides are methyl groups.

4. The oligonucleotide of claim 1, wherein the 5'-O-alkyl nucleotide is a 5'-O-alkyl thymidine.

5. The oligonucleotide of claim 1, wherein the 5'-O-alkyl nucleotide is linked to X^1 via a phosphodiester linkage or a phosphorothioate linkage.

6. The oligonucleotide of claim 1, wherein group Z is linked to X^2 via a linkage selected from the group consisting of a phosphotriester linkage, a phosphorothioate linkage, and a phosphoramidate linkage.

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7. The oligonucleotide of claim 1, wherein Z is a 3-to-3' linked nucleotide.

8. The oligonucleotide of claim 1, wherein the segment X^1–Y–X^2 has a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-24.

9. A composition useful for inhibiting expression of a target gene in a subject, comprising a chimeric oligonucleotide as recited in claim 1 in a pharmaceutically acceptable vehicle.

10. The composition of claim 9, wherein the vehicle includes a lipid-cationic peptoid conjugate of the formula:

L–linker–[$N(CH_2CH_2NH_2)CH_2(C=O)$-$N(CH_2CH_2R)CH_2(C=O)$-$N(CH_2CH_2R)CH_2(C=O)]_3$-NH_2

where

L is selected from a lipid moiety comprising at least one fatty alkyl or alkenyl chain between about 8 and 24 carbon atoms in length and a steroid;

each group R is independently selected from alkyl, aminoalkyl, and aralkyl, and

the linker is selected from the group consisting of a direct bond, an oligopeptide, a substantially linear alkyl chain from 2 to about 30 bonds in length, and a substantially linear chain from 2 to about 30 bonds in length consisting of alkyl bonds and one or more linkages selected from the group consisting of ester, amide, carbonate, carbamate, disulfide, peptide, and ether.

11. The composition of claim 10, wherein the linker is from 3 to about 15 bonds in length.

12. The composition of claim 10, wherein said fatty alkyl or alkenyl chain is between about 14 and 24 carbon atoms in length.

13. The composition of claim 10, wherein L is a phospholipid group, having two fatty alkyl or alkenyl chains between about 8 and 24 carbon atoms in length.

14. The composition of claim 10, wherein L is a cholesteryl group.

15. The composition of claim 10, wherein R is isopropyl or 4-methoxyphenyl.

16. The composition of claim 10, wherein the lipid-cationic peptoid conjugate is of the formula:

$L–(CH_2)_n$-(C=O)-$[N(CH_2CH_2NH_2)CH_2(C=O)$-$N(CH_2CH_2R)CH_2(C=O)$-$N(CH_2CH_2R)CH_2(C=O)]_3$-$NH_2$,

where

L is selected from (i) a phosphatidylethanolamino group, having fatty alkyl or alkenyl chains between about 8 and 24 carbon atoms in length, and (ii) a cholesteryl group linked to the adjacent $-(CH_2)_n-$ segment by an ester, amide or carbamate linkage;

n is 1-5; and

R is selected from isopropyl and 4-methoxyphenyl.

17. The composition of claim 16, wherein the lipid-cationic peptoid conjugate is selected from the group consisting of compounds represented herein as:

(a) Lipitoid 1, or DMPE(NaeNmpeNmpe)$_3$;

(b) Lipitoid 2, DMPE(NaeNiaNia)$_3$;

(c) Cholesteroid 1, or Chol-β-ala-(NaeNmpeNmpe)$_3$;

(d) Cholesteroid 2, or Chol-Ahx-(NaeNmpeNmpe)$_3$;

(e) Cholesteroid 3, or Chol-β-ala-(NaeNiaNia)$_3$; and

(f) Cholesteroid 4, or Chol-Ahx-(NaeNiaNia)$_3$.

18. A method of inhibiting expression of a target gene in a subject, comprising administering to the subject, in a pharmaceutically acceptable vehicle, an amount of a chimeric oligonucleotide as recited in claim 1 which is effective to specifically hybridize to all or part of a selected target nucleic acid sequence derived from the gene.

19. The method of claim 18, wherein the target nucleic acid sequence is a mRNA derived from the target gene.

20. The method of claim 19, wherein the segment X^1–Y–X^2 of the chimeric oligonucleotide has a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-24.

21. The method of claim 18, wherein the vehicle includes a lipid-cationic peptoid conjugate as recited in claim 11.

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